REMARKS

I. Status of the Claims

Claims 1-67 were originally filed. As the result of a restriction requirement, claims 19-44, 51-62, 65, and 67 were withdrawn from consideration. Subsequently, these withdrawn claims along with claims 11, 63, and 64 were canceled. Currently, claims 1-10, 12-18, 45-50, and 66 are pending under examination.

In the Final Office Action mailed February 13, 2004, the Examiner indicated that claims 18 and 45-50 are allowed, whereas claims 2, 4, 5, 10, 12, 13, 15, 17, and 66 are allowable but for their dependency from claim 1, which has been rejected for alleged anticipation.

II. Claim Rejection

Claims 1, 3, 6-9, 14, and 16 remain rejected under 35 U.S.C. §102(b) for alleged anticipation by the Larsen *et al.* reference. Applicants respectfully traverse the rejection.

To support the anticipation rejection, all limitations of independent claim 1 must be provided expressly or implicitly by the Larsen *et al.* reference. Claim 1 is drawn to a method for increasing the mutation rate of a retrovirus or flavivirus. The method comprises the step of administering to a virally infected cell an RNA nucleoside analog, which has the following characteristics:

1. it is incorporated by a polymerase into an RNA copy of a genomic nucleic acid encoding the retrovirus or flavivirus;

2. it replaces a naturally occurring nucleotide; and

3. it complements a nucleotide different from the complement of the naturally occurring nucleotide it has replaced, thereby inducing the retrovirus or flavivirus to mutate.

The Examiner has not shown that all limitations of claim 1 are present in Larsen *et al.* In particular, the reference does not teach or suggest that the RNA nucleoside analog has a complement nucleotide different from the complement nucleotide of the naturally occurring nucleotide replaced by the analog. Mutations of nucleic acids occur when nucleotides in one

strand of a polynucleotide are altered and their complement nucleotides in the complementary strand are consequently altered through DNA or RNA synthesis. If a nucleotide analog is incorporated into one strand of a polynucleotide and replaces a naturally occurring nucleotide, yet the analog's complementary nucleotide remains unchanged in the subsequent synthesis of the complementary strand, then no sustainable mutation has occurred to the nucleic acid. Thus, it is necessary for the operability of the claimed method that a different complement base result from the replacement of a naturally occurring nucleotide by an RNA nucleoside analog.

The Examiner pointed to sections of the Larsen and Hamelin references where viral RNA shows gel mobility shift following toyocamycin (TMC) treatment as evidence of the incorporation of TMC into viral RNA in place of adenosine and concluded that this incorporation itself is a mutation (page 4 of the Final Office Action mailed February 13, 2004). Applicants do not dispute the TMC incorporation in the viral RNA, but cannot agree that such incorporation / substitution of adenosine alone amounts to the mutation within the scope of the pending claims, because the mutation as defined by the pending claims requires not only the mutation of the adenosine bases themselves but also the mutation of their complementary bases. As discussed above, a mutation that contributes to the increased mutation rate of a virus is a permanent and sustainable one, which requires an altered complementary nucleotide due to an initial base substitution. In this respect, even the Examiner herself acknowledged that it is not clear from the results of Larsen *et al.* and Hamelin *et al.* whether or not the mutation rate of the virus is increased (page 4 of the Final Office Action).

In rejecting the pending claims, the Examiner appears to rely on an inherency theory, *i.e.*, Larsen *et al.* inherently disclose the missing limitation that the RNA nucleoside analog complements a nucleotide different from the complement of the naturally nucleotide the analog has replaced. For instance, in exploring the possible mechanism of TMC action as an antiviral drug, Hamelin *et al.* offer a discussion on how TMC affects synthesis of viral proteins. The authors report that the presence of TMC does not appear to hinder the viral protein synthesis (the bridging paragraph between pages 492 and 493 of Hamelin *et al.*). In the same paragraph, the authors state,

> Toyocamycin is incorporated into all RNA species studied so far in mammalian cells and one of the questions we asked was whether incorporation of the analogue in lieu of some adenosine residues in mRNAs would bring about some misreading frame. The answer seems to be no, at least for the viral messenger RNAs we, and others, studied.
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> .. ..
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> We observe all the viral messenger RNAs and the viral proteins of a retrovirus synthesized and yet there is no virus release. It may very well be that some specific cellular functions such as those involved in glycosylation are necessary for the assembly and budding process for retrovirus production.

It is thus established that TMC incorporation in viral mRNA does not cause reading frame shift and that one of skill in the art believes that TMC's antiviral activity is based on a mechanism other than causing mutations in viral nucleic acids and interfering with viral protein synthesis. The Examiner, however, insisted in the Final Office Action that the reported lack of detectable reading frame shift in TMC-incorporated mRNA does not eliminate the possibility of point mutations in a viral nucleic acid caused by TMC incorporation (page 4 of the Final Office Action).

Yet, ***an anticipatory inherent feature must be a consistent, necessary, and inevitable occurrence and not a mere possibility or probability***. According to the Federal Circuit, "[i]nherency ..... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. v. Monsanto Co.*, 948 USPQ2d 1746, 1749 (Fed. Cir. 1991). "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation." *Transclean Corp. v. Bridgewood Services, Inc.*, 62 USPQ2d 1865 (Fed. Cir. 2002). The Examiner has not shown that the missing limitation as an invariable occurrence and thus has not provided sufficient support for a conclusion of anticipation based on inherency.

As Dr. Loeb attests in his declaration pursuant to 37 C.F.R. §1.132, the observations by Larsen *et al.* and Hamelin *et al.*, *i.e.*, that TMC appears to incorporate into viral

RNA but no reading frame shift is observed, strongly indicate to one of skill in the art that the replacement of adenosines by TMC in viral RNA does not lead to the changes in the incorporation of complementary nucleotides and hence any permanent, sustainable mutation, the type of mutation defined by the pending claims (Paragraph 7 of the declaration).

Furthermore, Applicants contend that the observations by Larsen *et al.*, Hamelin *et al.*, and others in studies involving TMC inhibition of viral replication do not support the conclusion that TMC incorporation in viral RNA causes changes in the incorporation of complementary nucleotides and sustainable mutations. Dr. Loeb attests in his declaration that, if the Examiner's assertion is correct, each viral RNA synthesized subsequent to TMC exposure would contain numerous point mutations. If such multiple point mutations indeed occurred, it is highly probable that they would result in detectable changes to the characteristics of the RNA, such as changes in splicing pattern, reading frame, viral protein synthesis, and/or viral protein activity (Paragraph 9 of the declaration). Yet, Hamelin *et al.* reported no detectable reading frame shift. According to Mauchauffe *et al.* (*Biomedicine*, 1979, **31**:17-20, Exhibit A of the declaration), reverse transcriptase activity remained unchanged from TMC treatment when an exogenous oligonucleotide template was used to eliminate the effect from TMC modified endogenous viral polynucleotide template (pages 18-19 of the Mauchauffe *et al.* reference). This observation is further confirmed by Moyer and Holmes (*Virology*, 1979, **98**:99-107, Exhibit B of the declaration), whose studies indicated that TMC treatment had no obvious effect on the synthesis and biological function of all five viral proteins in vesicular stomatitis virus (VSV) (see, *e.g.*, page 106 of the Moyer and Holmes reference) (Paragraphs 10 and 11 of the declaration).

Dr. Loeb thus concludes that, based on the above discussed studies, the major effect of the rA → TMC substitutions in viral RNA is not that which leads to changes in the sequence of the complementary nucleotides, which are required to cause nucleic acid mutations as defined by the pending claims of this application. The Examiner's assertion that rA → TMC substitutions reported by Larsen *et al.* lead to point mutations in the nucleic acids is not supported by the observations made by several research groups. Without further evidence, one

of skill in the art would not believe that such point mutations are a consistent, necessary, and inevitable occurrence to TMC incorporation in viral nucleic acids and that the accumulation of these point mutations is the mechanism of inhibition of viral RNA synthesis by TMC (Paragraph 12 of the declaration).

In summary, the Examiner has not established a *prima facie* case of anticipation, since all claim limitations are not found in the Larsen *et al.* reference. Neither has the Examiner established anticipation by inherency, since the presence of the missing element has not be shown to be a consistent, necessary, and invariable occurrence. Most importantly, by Dr. Loeb's declaration, Applicants have established that the reports by Larsen *et al.*, Hamelin *et al.*, Mauchauffe *et al.*, and Moyer and Holmes do not support a conclusion that the substitution of adenosine by TMC causes point mutations within the meaning of the pending claims, and that even if such point mutations do occur, they are certainly not an inherent characteristic of TMC incorporation in viral RNA, and their accumulation is not the mechanism of viral inhibition by TMC.

As such, Applicants respectfully request the withdrawal of the anticipation rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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